IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jane Hirsh, Alexander M. Klibanov, Timothy M. Swager, Stephen L. Buchwald, Whe Yong Lo, Alison B. Fleming, and Roman V. Rariy

Serial No.: 10/614,866 Art Unit: 1615

Filed: July 7, 2003 Examiner: Lakshmi Sarada Channavajjala

For: *ABUSE-DETERRENT PHARMACEUTICAL COMPOSITIONS OF OPIOIDS AND OTHER DRUGS*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND DECLARATION UNDER 37 C.F.R. 1.132

Sir:

I, Alison B. Fleming, hereby declare:

1. I affirm the statements made in my Declaration under 37 C.F.R. 1.132 filed July 7, 2007, in the above-identified patent application.

2. I participated in the telephone interview with the Examiner and her supervisor on November 6, 2007.

3. As discussed in the interview, Collegium, the assignee of this application, recently completed a proof of concept clinical study on formulations of oxycodone covered by the pending claims.

4. Clinical Study Design and Goals

A single dose, open-label, controlled, cross-over comparison study was conducted in 12 healthy volunteers to evaluate the following: (1) safety and pharmacokinetics of two formulations of our composition as compared to a marketed reference product (OxyContin®), (2) effect of food on pharmacokinetics, and (3) influence of tampering on pharmacokinetics (subjects chewed the dosage form before administration, a common method of misuse).

5. Clinical Study Results

When administered to fed subjects, both of our capsule formulations resulted in a plasma exposure similar to OxyContin®. Our formulation demonstrated a food effect, with the plasma levels in the fasted state being lower than those in the fed state. One of our formulations was administered to patients following chewing of the formulation (as a controlled simulation of misuse). The plasma profile for the chewed capsule contents was bioequivalent (as measured by C_{max} and AUC) to the capsule when administered whole and as intended, suggesting that misuse by chewing would not result in a spike in plasma level as desired by the abuser.

6. Conclusions

My previous Declaration demonstrated that the claimed composition differs in structure from the formulations claimed in the prior art. Further, the Declaration demonstrated that the claimed composition can protect incorporated drug from immediate release *in vitro* (specifically in simulated gastric fluid) after the formulation is crushed. The clinical results described herein demonstrate that a capsule formulation covered by

the pending claims (a) can produce therapeutic blood levels in humans when taken whole (as intended) by patients postprandially and (b) does not produce a spike in plasma concentration, as desired by an abuser, in a controlled simulation of misuse (i.e., by chewing).

7. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11/15/07

Alison B. Fleming, PhD